REMARKS/ARGUMENTS

The following remarks are fully responsive to the Office Action set forth above. Claims 28-32 are pending. Claim 28 is amended.

Objections

At the request of the Examiner, Applicants have amended the Abstract and Specification to correct various informalities. The Applicants submit that the amendments to the Abstract and Specification are supported by the Specification and claims as originally filed and do not introduce new matter.

Claim Rejections – 35 U.S.C. § 112, 2nd paragraph

Claims 28-32 are rejected under § 112, 2nd paragraph as being indefinite for failing to particularly point put and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action states that claim 28 is indefinite because it is not known what is meant by "determining residue identities ... using computer modeling." Claim 28 is amended to eliminate the "using computer modeling" language. This amendment clarifies and clearly defines the subject matter of the claimed invention. Support for this amendment can be found throughout the Specification, particularly in Example 1. Example 1, paragraph [0067], states "[b]y comparing ...sequences ...in the Kabat database." No new matter has been added. Applicants respectfully request that the amendment be entered.

Claims 28-32 are further rejected as indefinite under § 112, 2nd paragraph. The Office Action stated that the preamble of claim 28 is not clear whether both the humanized heavy and light chain variable domains or only one humanized variable domain of the humanized antibody is designed according to the claimed method. The preamble of claim 28 is amended to clarify that amino acid sequences of the variable domains of both heavy and light chain regions of the resultant humanized antibody are designed according to the claimed method. Support for this amendment is found through out the Specification and in particular Example 1. No new matter has been added. Applicants respectfully request that the amendment be entered.

Claim Rejections – 35 U.S.C. § 112, 1st paragraph

Claims 28-32 are rejected under 35 U.S.C. § 112, 1st paragraph as failing to comply with the written description requirement. The Office Action stated that claims 28-32 have introduced new matter. Applicants traverse this rejection.

A description is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. *See* MPEP 2163.04.

The present Specification, including the references incorporated therein, discloses in detail the method of designing amino acid sequences of a variable domain of a humanized monoclonal antibody.

As previously noted, support for claims 28-32 can be found throughout the Specification. In particular, support for steps (a), (b), (c), (d) and (e) of claims 28 can be found in the specification at paragraph [0043]. Additional support for step (d) of claim 28 can be found in the specification at paragraph [0067], last sentence. Support for claim 29 can be found in the specification at paragraphs [0043] and [0067]. Support for claim 30 can be found in the specification at paragraphs [0043] and [0067]. Support for claim 31 can be found in the specification at paragraph [0043], last sentence. Support for step (f) of claim 32 can be found in the specification at paragraph [0044], first sentence and Examples 2 and 3. Support for step (g) of claim 32 can be found in the specification at paragraphs [0044, 0045 and 0046]. Support for step (h) of claim 32 can be found in the specification at paragraph [0053]. Support for step (i) of claim 32 can be found in the specification at paragraph [0048]. The Specification clearly provides written description support for the features recited in claims 28-32, and thus, no new matter has been introduced. Furthermore, the Specification demonstrates that Applicants were in possession of each step of the claimed method as of the filing date of the present application.

The Office Action also stated that there was inadequate written support for claims 28-32 because the disclosure only contemplated humanization of the LL2 antibody. Applicants respectfully traverse this rejection.

It is not required for purposes of Section 112, 1st paragraph that Applicants be in possession of every possible species of humanized antibodies encompassed within the genus of the claimed method. While a certain amount of experimentation might be required to determine amino acid sequences to design a humanized monoclonal antibody, the method of determining, selecting, incorporating, retaining and finally obtaining the desired amino acid sequences in the designing of

humanized monoclonal antibodies are described in detail in the Specification. Moreover, the various steps recited in the claims are well known in the art and a matter of routine experimentation for the person of ordinary skill in the art.

The Office Action further stated that there was inadequate written support for the human framework regions that have approximately 75 to 92.3% sequence identity with the framework regions in the monoclonal antibody to be humanized. While the Specification clearly discloses at paragraph [0043] the residue identity range of 75 to 92.3%, the Office Action is of the view that this range applies only to the light chain framework regions. This interpretation is incorrect. At paragraph [0043], immediately following the residue identity range of 75 to 92.3% begins a new sentence with "similarly." The use of "similarly" clearly indicates that the range of sequence identities, disclosed in the preceding sentence, also applies to the heavy chain. Thus, there is adequate written support for the human framework regions that have approximately 75 to 92.3% sequence identity with the framework regions in the monoclonal antibody to be humanized.

The Office Action further stated that there was inadequate support for using computer modeling for determining residue identities between variable domains of the non-human monoclonal antibody and the human monoclonal antibodies, as recited in claim 28. Claim 28 is amended to eliminate the term "computer modeling," and hence, this rejection is moot.

Applicants respectfully request withdrawal of these rejections.

Claim Rejections – 35 USC § 103(a)

Claims 28-32 are rejected under 35 U.S.C. §103 (a) as being unpatentable over WO 90/07861 to Queen et al. ("Queen") in view of U.S. Patent 5, 859,205 to Adair et al. ("Adair"). Applicants respectfully traverse the rejection.

Queen does not make obvious claim 28 because Queen does not teach or suggest selecting human framework regions from two or more variable domains wherein each selected human framework region has a sequence identity of 75-92.3% to the corresponding framework regions of the non-human monoclonal antibody to be humanized. In fact, the Office Action states that "Queen et al. do no specifically teach selecting human framework regions from two or more variable domains wherein each selected human framework region has a sequence identity

of approximately 75 to 92.3% to the corresponding framework regions of the donor antibody (i.e. non-human monoclonal antibody to be humanized)."

A prima facie case of obviousness requires: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or combine the teachings; 2) a reasonable expectation of success; and 3) the prior art reference or references must teach or suggest all the claim limitations. [MPEP 2143] By this standard, the Office Action has failed to establish a prima facie case of obviousness.

According to the Office Action, Adair overcomes the deficiencies of Queen. Adair, however, does not overcome the deficiencies of Queen. While the Office Action cites Adair for disclosing antibody humanization using framework regions selected from two different human variable domains, Adair does not teach or suggest that the selected human framework regions have a sequence identity of 75-92.3% to the corresponding framework regions of the non-human monoclonal antibody to be humanized. Rather, Adair discloses only a hierarchy of positions identified "within the framework of the variable regions (i.e. outside both the Kabat CDRs and structural loops of the variable regions) at which the amino acid identities of the residues are important for obtaining CDR-grafted products with satisfactory binding affinity." Column 3, lines 49-53. In fact, at a number of locations in the Specification, Adair states that their "protocol for obtaining satisfactory CDR-grafted products may be applied very widely irrespective of the level of homology between the donor immunoglobin and acceptor framework." Column 3, lines 54-57. Further at column 6, lines 18-20, Adair states, "[h]owever, a high level of homology between donor and acceptor sequences is not important for application of the present invention. At column 6, lines 28-29, Adair reiterates that "the present invention is applicable to any combination of donor and acceptor antibodies irrespective of the level of homology between their sequences." Clearly, Adair does not teach or suggest the recited sequence identity range of 75-92.3% between the framework work regions of the human variable domain and the monoclonal antibody to be humanized.

Because neither Queen nor Adair teach or suggest the recited sequence identity range of 75-92.3% between the framework work regions of the human variable domain and the monoclonal antibody to be humanized, one of ordinary skill in the art would not be motivated to combine the references.

For at least these reasons claim 28 should be reconsidered and the rejection withdrawn. Because claims 29-32 depend from independent claim 28, claims 29-32 are also allowable for at least the reasons discussed above.

In addition, with respect to claim 31, neither Queen nor Adair alone or in combination teach or suggest that that the selected amino acid residues of step (d) are within 4.5 Angstrom radius of all atoms within each CDR regions of the light and heavy chain of the resultant humanized monoclonal antibody.

Conclusion

All pending claims are now in condition for allowance. A notice to that effect is respectfully requested.

Respectfully Submitted,

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